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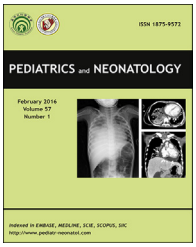

ORIGINAL ARTICLE

Serum Lactate, Brain Magnetic Resonance Imaging and Outcome of Neonatal Hypoxic Ischemic Encephalopathy after Therapeutic Hypothermia

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Background: Serum lactate was used to predict the severity and outcome of neonatal hypoxic ischemic encephalopathy (HIE) before the era of therapeutic hypothermia (TH). There is no report on neurodevelopment (ND) outcome of neonates with HIE treated with TH in Taiwan.
Methods: Between April 2011 and December 2012, newborn infants admitted to Chang Gung Memorial Hospital (CGMH), with gestational age $>$ 35 weeks and birth weight $\geq$ 1800 g, who had acute perinatal events, evidence of significant fetal compromise, and ongoing clinical encephalopathy were prospectively enrolled for TH. Whole body cooling method was used to maintain the affected neonate's esophageal temperature at 33.5 $\pm$ 0.5°C for 72 hours. Demographic data were recorded and hemogram, biochemical parameters, serum lactate, and creatine kinase (CK) were measured as well. Brain magnetic resonance imaging (MRI) was performed between 7 and 14 days of life. ND outcome of infants was evaluated by Bayley Scales of Infant Development, third edition (BSID-III) at 24 months of corrected age. Poor ND (PND) outcome was defined as infants surviving with either disability or ND delay.
Results: Seventeen patients were enrolled. Fifty-nine percent of babies (10/17) were born through cesarean section and 77% of babies (13/17) were transferred from outside hospitals. Six babies were moderate HIE and 11 babies were severe HIE. Among the 14 surviving patients,

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eight infants had PND outcome. There was no difference in demographic data between infants with and without PND. Serum level of lactate (mg/dL) after 72 hours of TH was higher (35.6 vs. 13.8, $p = 0.042$) in infants with PND. Neonates with abnormal brain MRI findings were also associated with PND ($p = 0.01$).

Conclusion: This is the first report on ND outcome of neonates with HIE treated with TH in Taiwan. Higher serum level of lactate following TH and abnormal results of brain MRI are associated with poor ND outcome.

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1. Introduction

Perinatal asphyxia and neonatal hypoxic ischemic encephalopathy (HIE) are associated with high morbidity and mortality rates worldwide.[1,2] Current evidence and guidelines recommend that newly born infants born at or near term with evolving moderate to severe HIE should be offered therapeutic hypothermia (TH).[3–6] Used clinically, TH improves both survival and the neurologic outcomes of those who survive, but the effect is only modest.[7–10] Adjuvant therapies combined with TH are emerging and may improve the outcome of neonates with HIE.[11–13] Hence, it is important to study biomarkers of neonatal HIE which can be used to monitor severity of illness or therapeutic effects when discovering new therapies.

TH for neonatal HIE was introduced into Taiwan in 2010 and only 35.5% of moderate to severe HIE patients received TH between January 2010 and November 2011 in Taiwan.[14] To date, there are no neurodevelopment (ND) outcome data of neonates with HIE treated with TH in Taiwan. The aim of the study was to describe our experiences of TH in managing neonates with HIE and to report the ND outcome of affected infants. In addition, we collected and analyzed parameters and biochemical markers to discover factors associated with the ND outcome.

2. Materials and methods

This prospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH) and was conducted in the neonatal intensive care unit (NICU) at CGMH during the period between April 2011 and December 2012. CGMH is a medical center in the northern part of Taiwan which has approximately 3000–4000 deliveries annually and a level III NICU with 37 intensive care beds as well as 70 intermediate beds. CGMH has an active neonatal transport team and one sixth of the NICU admissions were through neonatal transport. Most of the outside hospitals are located within 30–60 minutes' drive from our hospital.

Newborn infants with gestational age > 35 weeks and birth weight ≥ 1800g, who were affected with moderate to severe HIE,[15] and met the criteria for TH were enrolled. Eligibility criteria were in accordance with the National Institute of Child Health and Human Development trial[7] with modification (Figure 1 and Table 1). In brief, affected infants should have acute perinatal events, evidence of significant fetal compromise, and ongoing clinical encephalopathy. The exclusion criteria in this study include major congenital anomaly, intracranial hemorrhage, availability of 1st hour blood gas with pH > 7.15 and base deficit <10, and refusal of therapy by family.

Once the infant fulfilled the criteria, TH would be commenced within 6 hours of life. Affected newborn infants were cooled by Blanketrol II (Hyper-Hypothermia System, Cincinnati Sub-Zero, Cincinnati, OH) to maintain their esophageal temperature at 33–34°C for 72 hours.[7] Patients would be sedated if they were shivering or became irritable. The patients then were rewarmed slowly (< 0.5°C/h) to 36.5°C. During the hypothermic period, vital signs were recorded every 30 minutes in the first 4 hours, every 60 minutes in 4–12 hours, and every 2 hours in the 12–72 hours. Hemograms, electrolytes, blood sugar, blood gas analysis, creatine kinase (CK), lactate, as well as liver and renal functions, were measured regularly.

Amplitude integrated electroencephalography was used to monitor seizures. Antiepileptic drugs would be prescribed if there was either a clinical or electrographic seizure. Brain ultrasonography was performed before TH to exclude intracranial hemorrhage and congenital anomalies, and brain magnetic resonance imaging (MRI) was performed between 7 and 14 days of age. Abnormal MRI findings were defined as the presence of abnormal signals of the posterior limb of the internal capsule, the basal ganglia, thalami, or watershed areas.

Bayley Scales of Infant Development, third edition (BSID-III) were used to assess ND outcome of surviving infants. Neurodevelopmental delay was defined as presence of any one of the following domains: cognitive scores < 85, language scores < 79, and motor scores < 85 at 24 months of corrected age. In this study, PND outcome was defined as surviving infants with one or more of the following: disability (cerebral palsy, bilateral blindness, or bilateral hearing loss) or delay (no disability but with lower BSID-III scores, defined as previous description).

Statistical analysis was performed with SPSS Statistics version 20 (IBM, Armonk, NY). Continuous variables were analyzed by Mann-Whitney U test and categorical variables were analyzed by Fisher's exact test. Data were presented as median (range). A p value < 0.05 indicated statistical significance.

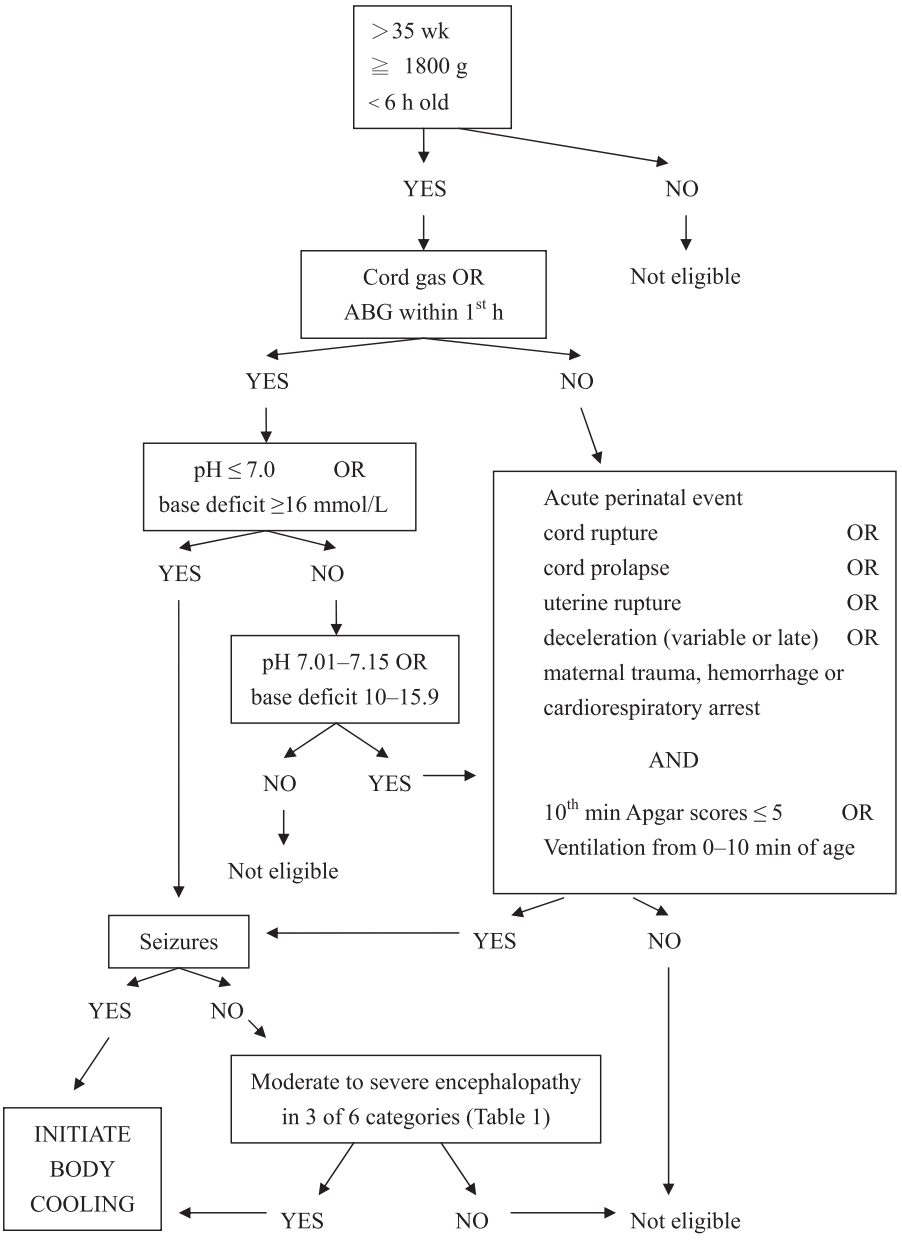

Figure 1 Eligibility criteria for therapeutic hypothermia in neonates with hypoxic ischemic encephalopathy (HIE) at Chang Gung Memorial Hospital (CGMH). ABG = arterial blood gas.

3. Results

Seventeen patients were enrolled in the study, 10 of whom were baby boys. Fifty-nine percent of babies (10/17) were born through cesarean section and 77% of babies (13/17) were transferred from outside hospitals. Six babies were moderate HIE (35%) and 11 babies were severe HIE (65%). The most common intrapartum complications associated with the development of HIE were fetal heart beat deceleration, followed by placenta abruption and tight nuchal cord.

During the study period, the age to start TH among affected neonates was 5 (2.9, 7.0) hours old. Seventy-seven percent of patients were transferred from outside hospitals and their age at admission was 148 (106, 324) minutes old. The age (minutes old) to start TH among inborn infants was 211 (173, 247) and was 309 (210, 421) among outborn infants ($p = 0.023$). The rewarm time for the cooling babies was 6.5 (6, 14) hours.

Three babies were moribund and were diagnosed as severe HIE. Apgar scores at 1 minute and 5 minute of them were 0 (0, 1) and 1 (0, 1), respectively. The pH level of first blood gas analysis was 6.5 (6.35, 6.53). Cardiopulmonary resuscitation (CPR) was performed for these three patients immediately after birth and the duration of CPR was 51 (12, 60) minutes. At the request of the family, two were still transferred to our hospital. All 17 patients completed 72 hours of TH without premature termination of TH. No mortality related to the TH occurred during the study period. Eighty-eight percent (15/17) of patients developed

Table 1 Diagnostic criteria for moderate or severe encephalopathy.

Category	Moderate encephalopathy	Severe encephalopathy
Level of consciousness	Lethargy	Stupor or coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Primitive reflexes	Weak suck or incomplete Moro reflex	Absent suck or Moro reflex
Autonomic system	Constricted pupils, bradycardia, or periodic/irregular breathing	Deviated/ dilated/ nonreactive pupils, variable heart rate, or apnea

Table 2 Demographic data and neurodevelopmental outcome.

	Without PND ($n = 4$)	PND ($n = 8$)	p
Gestational age (wk)	39.5 ± 0.6	37.9 ± 1.5	0.061
Birth weight (g)	2658 ± 465	3525 ± 828	0.084
Male/female (n)	4/0	4/4	0.208
Vaginal delivery/cesarean section (n)	0/4	3/5	0.491
Apgar score at 1 min	2 ± 1	2 ± 2	0.746
Apgar score at 5 min	4 ± 1	4 ± 3	0.733
Inborn/outborn (n)	1/3	2/6	1.0

PND = poor neurodevelopment.

seizure within 24 hours of life. Phenobarbital was used as the first line antiepileptic drug to treat neonatal seizure. Palliative therapy was given to all three moribund patients after TH and family meetings. Treatment was withdrawn within 10 days of life. Thus, the survival rate was 82% (14/17). The remaining 14 infants were discharged and followed in the outpatient department. Two infants lost follow-up. Both were baby boys, without CPR after birth, whose Apgar scores were 1 and 4 at 1 and 5 minutes, respectively, and who were diagnosed as moderate HIE. They received ND evaluation by BSID-III at 6 months of age and the scores were normal without any delay. Finally, 86% of surviving patients were followed to 24 months of age, and they were analyzed to study factors associated with ND outcome.

Eight infants had PND outcome in the study; 87.5% of them were severe HIE and 12.5% were moderate HIE. The demographic information, clinical features, and laboratory data of the infants with PND and without PND are depicted in Tables 2 and 3. Affected neonates with abnormal brain MRI findings were associated with the development of PND at 24 months of age (Table 3). Serum levels of lactate and CK were routinely measured in affected neonates before and after TH. In the study, we showed that serum level of lactate (mg/dL) after 72 hours of TH was higher (35.6 vs. 13.8, $p = 0.042$) in infants with PND comparing with infants without PND at 24 months of age (Table 3). The serum level of lactate after 72 hours of TH was 103.4 mg/dL for the patient who was affected with moderate HIE and had PND. By contrast, the serum level of lactate after 72 hours of TH was 11.5 mg/dL for the patient who was affected by severe HIE but was without PND at 24 months of age.

4. Discussion

Before the era of TH, newborn infants with moderate encephalopathy had a 20–35% risk of later sequelae from the insult, although those whose neurologic examinations were completely normal within 1 week had a good likelihood of normal outcome.[16] Infants with severe encephalopathy had a 75% risk of dying in the neonatal period, and among survivors, an almost universal risk of sequelae existed.[16–18] The results of the National Institute of Child Health and Human Development (NICHD) trial indicated that whole-body hypothermia reduced the risk of death or disability in infants with moderate or severe HIE.[7] By contrast, the results of the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial showed that TH did not significantly reduce the combined rate of death or severe disability in infants with moderate or severe HIE, but resulted in improved neurologic outcomes in survivors.[9] In the current small study, 16.7% of infants with moderate HIE had PND outcome. Among infants with severe HIE, 27.3% died and 87.5% of survivors had PND outcome. Ours is the first study to report ND follow-up data in infants with moderate to severe HIE receiving TH in Taiwan, and our results further support the current evidence[7,9,16–18] of beneficial effects of TH in treating neonatal HIE.

The duration of the latent phase or therapeutic window between primary and secondary energy failure secondary to hypoxic ischemic brain injury was noted to be approximately 6 hours in near term fetal sheep treated with hypothermia initiated at varying intervals following timed hypoxic ischemic injury.[12,19–21] In our study, the average age to start TH among affected neonates was 4.8 hours old. Not surprisingly, the time to start TH among inborn infants was earlier than that among outborn infants, but there was no difference in terms of ND outcome. If we used cutoff time of starting TH to < 3.5 or < 4 hours of age, there was also no difference (data not shown). In the TOBY trial, the relative risk for the primary outcome with cooling which was started < 4 hours after birth was 0.77 [95% confidence interval (CI), 0.44–1.04], whereas when cooling started between 4 and 6 hours after birth, the relative risk was 0.95

Table 3 Clinical features, laboratory data and neurodevelopmental outcome.

	Without PND ($n = 4$)	PND ($n = 8$)	p
HIE			0.067
moderate (n)	3	1	
severe (n)	1	7	
Seizure (n)			0.333
Yes/no	3/1	8/0	
Brain MRI findings (n)			0.01*
Normal/abnormal	4/0	1/7	
1st blood gas pH value	6.97 (6.73, 7.32)	7.02 (6.72, 7.43)	0.850
Lactate (0 h) (mg/dL)	162.5 (72.7, 191.8)	139.5 (32.2, 313.7)	0.734
Lactate (72 h) (mg/dL)	13.8 (11.5, 22.1)	35.6 (13.7, 103.4)	0.042*
Δ Lactate (%)	92.3 (69.6, 92.7)	70.0 (14.4, 87.5)	0.042*
CK (0 h) (IU/L)	2090 (712, 15323)	1630 (470, 8822)	0.705
CK (72 h) (IU/L)	1276 (446, 1969)	755 (73, 2318)	0.522
Δ CK (%)	51.6 (8.8, 87.2)	69.5 (19.1, 84.5)	0.522

Serum lactate and CK were measured before and after therapeutic hypothermia.
Continuous variables were presented as median (range) and analyzed by Mann-Whitney U test.
CK = creatine kinase; HIE = hypoxic ischemic encephalopathy; MRI = magnetic resonance imaging; PND = poor neurodevelopment.
*$p < 0.05$. Δ Lactate : Lactate (0 hour) − Lactate (72 hours)/Lactate (0 hour). Δ CK : CK (0 hour) − CK (72 hours)/CK (0 hour).

(95% CI, 0.72−1.25).[9] Hence, it is recommended that TH should be initiated before 6 hours of age, and as early as possible.[5,9]

Serum or plasma levels of lactate were used to predict severity and outcome of neonatal HIE before the era of TH.[22–26] It has been demonstrated that a plasma lactate concentration > 7.5 mmol/L (67.5 mg/dL) taken within 1 hour of life was associated with moderate or severe HIE with a sensitivity of 94% and specificity of 67%.[24] In a retrospective study of the Japanese National Center for Child Health and Development, serum levels of lactate and CK at admission were significantly higher in infants with poor outcome compared to those with favorable outcomes. The average levels of lactate and CK in the poor outcome group were 11.9 mmol/L (107.1 mg/dL) and 1022 IU/L.[26] Shah et al[24] also indicated that the highest recorded lactate level in the 1st hour of life and serial measurements of lactate were important predictors of moderate-to-severe HIE. We measured serum levels of lactate and CK within 6 hours of life as well as after TH in affected infants. Both the levels of lactate and CK of our patients were higher than those of the Japanese studies[26] indicating more severe illness, but the outcome was better than in the historical data.[16–18] We were unable to compare our data with that of Shah's study[24] equally, because nearly 80% of our patients were transferred from outside hospitals. Hence, levels of lactate were not all drawn and measured within the 1st hour of life. In addition, all of our patients underwent TH.

MRI can delineate the sites and extent of neuronal injury. Imaging predictors of risk of adverse outcome include absence of signals from the posterior limb of the internal capsule, ischemic damage to the basal ganglia, thalami, and watershed areas.[27,28] A nested substudy from the TOBY trial indicated that MRI could accurately predict outcome of neonates with HIE at 18 months of age in cooled and non-cooled infants.[29] Similar to the TOBY trial, our study showed that findings of MRI were associated with outcome of affected infants at 24 months of age.

Finer et al[16] indicated that neonates with moderate HIE whose neurologic examinations were completely normal within 1 week had a good likelihood of normal outcome before the era of TH. In a study recruiting 51 neonates with HIE, the best predictive value for neurological outcome at 24 months of age was seen with neurological examination at discharge (positive and negative predictive values of 86% and 72%, respectively).[30] In the current study, there were four patients with moderate HIE, whose neurological examinations were normal before discharge. As for the eight patients with severe HIE, the neurological examinations were abnormal before discharge. There was no significant difference between infants with normal and abnormal neurological examinations before discharge in terms of outcome.

The limitation of the current study is that the sample size is relatively small. In the era of TH, it is important to address the facts we mentioned as well as to search for and study biochemical parameters or biomarkers for the sake of monitoring severity of illness or therapeutic effects when treating patients or discovering new therapies.

This is the first report on neurodevelopmental outcome of neonates with HIE receiving TH in Taiwan. Based on our results, we conclude that in the era of TH, higher serum levels of lactate following TH and abnormal results of brain MRI are associated with poor neurodevelopmental outcome in neonates with HIE.

Conflicts of interest

The authors have indicated they have no personal financial relationships relevant to this article to disclose.

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